Drug safety of macrolide and quinolone antibiotics in a tertiary care hospital: administration of interacting co-medication and QT prolongation

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Abstract: PURPOSE Some macrolide and quinolone antibiotics (MQABs) are associated with QT prolongation and life-threatening torsade de pointes (TdP) arrhythmia. MQAB may also inhibit cytochrome P450 isoenzymes and thereby cause pharmacokinetic drug interactions (DDIs). There is limited data on the frequency and management of such risks in clinical practice. We aimed to quantify co-administration of MQAB with interacting drugs and associated adverse drug reactions. METHODS We conducted an observational study within our pharmacoepidemiological database derived from electronic medical records of a tertiary care hospital. Among all users of MQAB associated with TdP, we determined the prevalence of additional QT-prolonging drugs and risk factors and identified contraindicated co-administrations of simvastatin, atorvastatin, or tizanidine. Electrocardiographic (ECG) monitoring and associated adverse events were validated in medical records. RESULTS Among 3444 administered courses of clarithromycin, erythromycin, azithromycin, ciprofloxacin, levofloxacin, or moxifloxacin, there were 1332 (38.7 %) with concomitant use of additional QT-prolonging drugs. Among those, we identified seven cases of drug-related QT prolongation, but 49.1 % had no ECG monitoring. Of all MQAB users, 547 (15.9 %) had hypokalemia. Forty-four MQAB users had contraindicated co-administrations of simvastatin, atorvastatin, or tizanidine and three of those related adverse drug reactions. CONCLUSION In the studied real-life setting, we found a considerable number of MQAB users with additional risk factors for TdP but no ECG monitoring. However, adverse drug reactions were rarely found, and costs vs. benefits of ECG monitoring have to be weighted. In contrast, avoidable risk factors and selected contraindicated pharmacokinetic interactions are clear targets for implementation as automated alerts in electronic prescribing systems.

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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Drug Safety of Macrolide and Quinolone Antibiotics in a Tertiary Care Hospital: Administration of Interacting Comedication and QT-Prolongation

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ABSTRACT

Purpose Some macrolide and quinolone antibiotics (MQAB) are associated with QT-prolongation and life-threatening torsade de pointes arrhythmia (TdP). MQAB may also inhibit cytochrome P450 isoenzymes and thereby cause pharmacokinetic drug-drug interactions (DDI). There is limited data on the frequency and management of such risks in clinical practice. This study aimed to quantify co-administration of MQAB with potentially interacting drugs and associated adverse drug reactions.

Methods We conducted an observational study within our pharmacoepidemiological database derived from electronic medical records of a tertiary care hospital. Among all users of MQAB associated with TdP we determined the prevalence of additional QT-prolonging drugs and risk factors for TdP, and identified contraindicated co-administrations of simvastatin, atorvastatin or tizanidine. ECG-monitoring and associated adverse drug reactions were validated in medical records.

Results Among 3444 administered courses of clarithromycin, erythromycin, azithromycin, ciprofloxacin, levofloxacin or moxifloxacin there were 1332 (38.7 %) with concomitant use of additional QT-prolonging drugs. Among those we identified 7 adverse drug reactions related to QT-prolongation, but 49.1 % had no ECG-monitoring. Of all MQAB users 547 (15.9 %) had hypokalemia. Forty-four MQAB users had contraindicated co-administrations of simvastatin, atorvastatin or tizanidine, and 3 of those related adverse drug reactions.

Conclusion In the studied real-life setting we found a considerable number of MQAB users with additional risk factors for TdP but no ECG monitoring. However, adverse drug reactions were rarely found, and costs vs. benefits of ECG monitoring have to be weighted. In contrast, avoidable risk factors and selected contraindicated pharmacokinetic interactions are clear targets for implementation as automated alerts in electronic prescribing systems.

INTRODUCTION

Macrolide and quinolone antibiotics (MQAB) are among the most frequently prescribed drugs that are associated with life-threatening torsade de pointes (TdP) cardiac arrhythmia [1-5]. Information on the assessment of their potential risk to cause TdP vs. therapeutic benefits are featured in their Summary of Product Characteristics (SPC) and other resources such as guidelines, websites and clinical decision support software [6, 7]. Patients' resilience to drug-induced TdP is often described as 'repolarization reserve', referring to the ventricle's capacity to compensate delayed repolarization [8]. Prolongation of the QT-interval is an important predictor of TdP, and ECG monitoring is therefore indicated in patients exposed to QT-prolonging drugs with a high risk of TdP. The risk is partially dose-dependent and highest in patients with concomitant administration of several QT-prolonging drugs. Indeed, in clinical practice patients with drug-associated TdP had typically been exposed to several risk drugs. TdP is also associated with additional factors including high age, female sex, hypokalemia, heart diseases and renal impairment [9-11]. If the QTc interval exceeds 500 ms or there is a drug-associated increase by more than 60 ms, QT-prolonging drugs should usually be discontinued [12]. However the risk of TdP may already be increased at QTc intervals above the upper limit of normal, which is commonly defined as 450 ms for men and 460 ms for women [13]. Inpatients of a tertiary care hospital may frequently feature reduced repolarization reserves due to polypharmacy and other risk factors for TdP. Therefore, awareness of TdP-inducing drugs and careful ECG monitoring are important parts of proactive drug safety management in this population [14]. Furthermore, some MQAB are also well known for avoidable pharmacokinetic DDI [15, 16]. Clarithromycin, erythromycin and ciprofloxacin are strong inhibitors of cytochrome P450 isoenzymes (CYP). Their co-administration with certain substrates may outweigh any potential benefits, especially if 'victim-drugs' are prescribed in high doses and if therapeutic alternatives are available. The latency time of resulting

adverse drug reactions (ADR) has a broad range. DDI with MQAB may lead to simvastatin-induced rhabdomyolysis only after several weeks of co-administration [17-19], whereas ciprofloxacin may cause a 7- to 10-fold increase of tizanidine c_{max} and AUC within 24 hours and result in severe hypotension and reduced psychomotor functions [20].

The present study aimed to quantify co-administration of MQAB with QT-prolonging and other potentially interacting drugs, relevant risk factors and the frequency of associated adverse drug reactions in the real-life setting of hospitalized patients.

METHODS

Data Source

The study was conducted using data from the calendar year 2012 of our previously described comprehensive pharmacoepidemiological hospital database [21]. The database contains information on electronic drug prescriptions, demographics, laboratory results and diagnoses for hospitalized patients of a Swiss tertiary care hospital. For the assessment of ECG monitoring and outcome validation of potential DDI we reviewed original electronic medical records unless patients had refused consent to use their data for research upon admission.

Study design

Selection of the study population and overall study design are presented in **Figure 1**. We conducted a retrospective observational study that analyzed usage patterns, ECG monitoring, potential DDI, laboratory data and relevant comorbidities in MQAB users of a tertiary care hospital. The cantonal ethics committee, the hospital's medical director and the hospital's center for clinical research had approved the data extraction, the setup and analysis of our anonymized pharmacoepidemiological database, and the access to original medical records for our research studies.

Usage patterns of QT-prolonging MQAB, co-administration of potentially interacting drugs and risk-factors for TdP

For the present study we developed, programmed and validated algorithms that searched our database for patients, patient-days and hospitalizations with exposure to MQAB and co-administered drugs of interest. Few hospitalizations with administration of two or more of the studied MQAB contributed to more than one exposure group and were accordingly counted more than once. We analyzed the following MQAB based on their established high potential to cause TdP according to information from their SPC and additional scientific resources [7, 22-25]: ciprofloxacin, clarithromycin, erythromycin, azithromycin, levofloxacin and moxifloxacin. For all users of those MQAB we identified additional co-administered drugs that also have an established high risk for QT-prolongation and TdP. Furthermore we identified selected drugs with well-documented relevant CYP-mediated pharmacokinetic interactions with the respective MQAB, i.e. concomitant administration of clarithromycin or erythromycin with simvastatin or high-dose atorvastatin (≥ 40 mg/d), and combined use of ciprofloxacin with tizanidine. Further algorithms identified additional risk factors for TdP. Current hypokalemia below 3.3 mmol/l or renal impairment with a decreased eGFR [26] that requires dose-reduction for clarithromycin, erythromycin, ciprofloxacin and levofloxacin. For patients with renal impairment we evaluated whether recommended dose-adjustments of the respective MQAB had actually been made [7]. Furthermore, we identified relevant cardiac comorbidities that may increase the risk of TdP based on documented ICD-10 codes of the following heart diseases: heart failure, cardiomyopathy, angina pectoris, myocardial infarction, heart murmurs, aortic stenosis, coronary artery stenosis, cardiac failure, QT prolongation, pacemaker implantation, ventricular septum defect, coronary interventions, palpitations, atrial

fibrillation or flutter, supraventricular arrhythmia, tachycardia, and tachy-bradycardia [3].

ECG-monitoring and evaluation of adverse events associated with potential medication errors

We assessed monitoring for QT-prolongation by reviewing all documented ECGs in patients' original medical records performed up to one week before (baseline) or during the co-administration of potentially interacting drugs for each hospitalization. A corrected QT interval (QTc) of >450 ms in men and >460 ms in women is associated with increased cardiovascular mortality and defined as the upper limit of normal by the American Heart Association. Longer QTc-intervals were accordingly categorized as 'abnormal QTc' for the present study [13, 27]. A QTc-interval above 500 ms significantly increases the risk of TdP and sudden cardiac death, and was defined as 'long QTc' [12]. For patients with abnormal and long QTc-intervals we reviewed the original ECG and comprehensive medical records for other, not drug-related contributing QTc-prolonging factors such as pacemakers, left bundle branch blocks or presence of tachycardia (heart rate >100/min). Only if no such confounders were identified, we assessed the causal relationship with the respective QT-prolonging drugs according to standardized WHO/CIOMS causality assessment criteria [28].

For the studied pharmacokinetic DDI involving simvastatin and atorvastatin we identified symptoms, signs and diagnoses of myopathy in comprehensive medical records including laboratory results of creatine kinase (CK) measurements [7]. For interactions involving tizanidine we evaluated any documentation of hypotension, drowsiness and reduced psychomotor functions [7].

Data analysis

Data analysis was descriptive with presentation of results in tables as appropriate. Frequencies were calculated with regard to individual patients, hospitalizations and patient-days. Data management and analyses were performed with STATA Version 13.1 (STATA Corporation, College Station, TX, USA).

RESULTS

Characteristics of the study population

Among 29969 patients from our database that had been hospitalized in 2012, 9777 (32.6%) had received treatment with systemic antibiotics. Amoxicillin-clavulanic acid was by far the most frequently used antibiotic (n=4112, 42.1%), and 29.1% of patients with systemic antibiotic treatment had received MQAB associated with TdP. Characteristics of the studied MQAB users and frequency distribution of different MQAB are presented in **Table 1**. Ciprofloxacin was the second most frequently used antibiotic in the hospital (19.2% of all patients with systemic antibiotic treatment) and by far the most frequently used MQAB. Mean and median duration of hospitalization for MQAB users were 19.2 and 5 days.

Co-medication of MQAB with additional QT-prolonging drugs, other risk factors for TdP and dose-adjustment in renal impairment

Co-medication of MQAB with other QT-prolonging drugs and prevalence of additional risk factors for TdP are presented in **Table 2**. Among 3444 courses of administered MQAB, additional drugs known to cause TdP were administered in 1332 (38.7 %). In 14.2% even two or more additional QT-prolonging drugs were administered. Some patients received up to 6 drugs known to cause TdP on the same day, frequently involving antiemetics, azole-antifungals and antidepressants. Patients using clarithromycin, azithromycin, levofloxacin or moxifloxacin were more frequently exposed to at least one additional drug known to cause TdP (between 51.5 and 60.4

%) than patients receiving erythromycin (29.9%) or ciprofloxacin (30.3 %). Current hypokalemia below 3.3 mmol/l, an important risk factor for TdP, was documented in 15.9%. For users of clarithromycin, erythromycin, ciprofloxacin and levofloxacin lack of recommended dose reduction of MQAB in the presence of impaired renal function was found in 122 (3.8 %) of administered courses. These occurred in 91 hospitalizations with ciprofloxacin (daily doses of >500 mg while eGFR <30ml/min or >1000 mg while eGFR 30-60 ml/min), in 16 hospitalizations with clarithromycin (daily doses of >500 mg while eGFR <30 ml/min), and in 15 hospitalizations with levofloxacin (daily doses of >250 mg while eGFR <20 ml/min or >500 mg while eGFR 20-50 ml/min). Approximately one in three patients exposed to the studied MQAB had a documented ICD-10 diagnosis of heart diseases associated with an increased risk for TdP.

ECG-monitoring in patients at risk for TdP

For 1332 administered MQAB courses with at least one additional QT-prolonging drug, medical records including performed ECGs could be further reviewed for 1236 (92.8%). Frequencies of ECG-monitoring and further risk factors for TdP in those patients are presented in **Table 3**. In 50.9 % adequate ECG monitoring was documented. Among hospitalizations with adequate ECG monitoring and abnormal QTc (n= 55), patients with non-drug causes for ECG abnormalities (n= 30), or patients with an ECG performed before exposure to the DDI (n= 12) were excluded from the CIOMS causality assessment. Thereafter 13 individual patients with an abnormal / long QTc interval remained for formal causality assessment. For 7 patients with QTc between 478 and 518 ms causality of the involved drugs known to prolong QT interval and cause TdP interval was classified as ‘possible’, and further details are presented in **Table 4**. We identified no episodes of TdP.

Pharmacokinetic interactions of MQAB with simvastatin, atorvastatin and tizanidine

Among the 546 individual patients taking clarithromycin or erythromycin we detected 9 patients with co-administration of simvastatin, 6 thereof taking 40 - 80 mg daily. An additional 22 patients were exposed to concomitant use of ≥40 mg atorvastatin daily. In none of these patients symptoms or signs of myopathy including elevated creatine kinase measurements indicated causally related adverse drug reactions.
Among the 2247 administered courses of ciprofloxacin we detected 13 with concomitant exposure to tizanidine, 5 thereof with ≥6mg/d. Three patients experienced episodes of hypotension shortly after this combination was administered, and 2 patients were treated with cardiac stimulants (etilefrine and midodrin), but without cessation of tizanidine-ciprofloxacin co-administration (**Table 4**). Causality for the decreases in blood pressure assessment in relation to the DDI was assessed as 'possible' in all three cases.

DISCUSSION

This study describes the use, co-medication and risk management of MQAB in the real-life setting of a tertiary care hospital with regard to TdP and to selected clinically relevant pharmacokinetic DDI. With the exception of ciprofloxacin, the studied potentially QT-prolonging MQAB were only used in a small proportion of patients. And ciprofloxacin is generally considered 'less torsadogenic' than other quinolones and was only recently added to the list of drugs with a known risk for TdP [2, 29, 30]. At the same time, it is remarkable how many MQAB users had additional risk factors for TdP. Most notably, more than one third were exposed to additional QT-prolonging drugs, and about one in six MQAB users also had hypokalemia, a risk factor that is usually easy to correct in hospitalized patients [12, 31]. Indeed, the SPC of clarithromycin features hypokalemia as an explicit contraindication to its use [7, 32], yet we detected 361 patient-days in which clarithromycin was administered despite current serum potassium below 3.3 mmol/l, representing 8.5 % of all patient-days

with exposure to clarithromycin. Renal impairment is another important risk factor for TdP, which may be explained by the reduced renal elimination of many drugs known to cause TdP and an increased risk for electrolyte disturbances [12]. We identified lack of dose-adjustment for renally eliminated MQAB. Although this concerned only a little less than 5% of MQAB users it represents a risk that can be avoided if physicians are aware of it at the time of prescription.

ECGs for the monitoring of abnormal or long QT intervals were available in about 50% in MQAB users with additional QT-prolonging co-medication. The higher proportion of patients with diagnosed heart diseases among the patients with adequate ECG monitoring may most likely be explained by confounding from the cardiac disease itself rather than a higher awareness for the drug-induced risk of TdP. A high proportion of patients without adequate ECG monitoring had at least one additional risk factors for TdP, and it is likely that additional cases of abnormal / long ECG remained undetected. On the other hand, medical records were searched for adverse drug reactions also in patients without ECG-monitoring, and overall only 7 cases of prolonged QTc between 478 and 518 ms were identified, and no case of TdP. The resources required for more intense and guideline-compliant ECG-monitoring must therefore be weighted against expected benefits. Some US tertiary care hospitals have successfully developed and introduced automated algorithms with subsequent alerts for ECG with QTc of >500 ms [33-36]. However, in order for such a system to be effective, a current plus a recent pre-treatment ECG are needed, and also pre-treatment ECGs must be justified [37, 38]. Our findings suggest that automated algorithms to improve the risk-assessment may include the following modifiable risk factors: hypokalemia, lack of dose adaptation to renal insufficiency, and ideally also suggestions for alternative co-medication. Nevertheless, the development of cost-effective ECG-monitoring algorithms and their implementation remains challenging, for MQAB users as well as for other high risk groups such as users of psychiatric drugs [39].

In comparison to QT-prolonging combinations, management implications of our findings regarding selected contraindicated combinations of MQAB with known pharmacokinetic interactions are straightforward. A high proportion of patients with such combinations had associated adverse drug reactions, and review of individual situations in original medical record showed that these combinations could have been avoided, as there would have been alternative management options in all cases. Rather simple automated simple alert-algorithms would therefore be an efficient preventive measure with a favorable relation of costs vs. benefits.

In conclusion our study found a considerable number of MQAB users with additional QT-prolonging co-medication and other risk factors for TdP in hospitalized patients, and a high proportion of those had no ECG monitoring. However, adverse drug reactions were rarely found, and benefits of intense ECG monitoring as well as benefits of QT-prolonging co-medication in MQAB users have to be weighted against costs. In contrast, correctable co-factors in MQAB users such as hypokalemia, lack of dose-adjustment in renal impairment and selected contraindicated pharmacokinetic interactions are clear targets for implementation as preventive automated alerts in electronic prescribing systems.

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Table 1: Characteristics of the study population

	Hospitalizations	
	n	(%)
All analyzed MQAB users	**3240**	**(100)**
Sex		
Male	1913	(59.0)
Female	1327	(41.0)
Age distribution		
<18	14	(0.4)
18-44	694	(21.4)
45-64	1195	(36.9)
65-84	1205	(37.2)
≥85	132	(4.1)
Use of studied antibiotics		
Macrolides		
Clarithromycin	476	(14.7)
Erythromycin	184	(5.7)
Azithromycin	113	(3.5)
Quinolones		
Ciprofloxacin	2247	(69.4)
Levofloxacin	321	(9.9)
Moxifloxacin	103	(3.2)
Units with highest use of MQAB		
Urology	677	(20.9)
Viszeral- and transplantation surgery	386	(11.9)
Internal medicine	381	(11.8)
Pneumology	271	(8.4)
Haematology	170	(5.2)
Most frequent primary ICD-10 diagnoses for hospitalizations with MQAB use		
Malignant neoplasms of lymphoid, hematopoietic and related tissue C81-C96	177	(5.5)
Complications of surgical and medical care, not elsewhere classified T80-T88	151	(4.7)
Other diseases of the urinary system N30-N39	142	(4.4)
Influenza and pneumonia J09-J18	139	(4.3)
Malignant neoplasms of digestive organs C15-C26	127	(3.9)

Table 2: Prevalences of QT-prolonging comedication and other risk factors for TdP in MQBA users

	Clarithromycin				Erythromycin				Azithromycin				Ciprofloxacin				Levofloxacin				Moxifloxacin			
	Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days		Hospitalizations		Patient-days	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Use of antibiotic	476	(100)	4238	(100)	184	(100)	901	(100)	113	(100)	725	(100)	2247	(100)	12989	(100)	321	(100)	2389	(100)	103	(100)	857	(100)
Co-medication with at least one QT-prolonging drug	282	(59.2)	3163	(74.6)	55	(29.9)	223	(24.0)	67	(59.3)	561	(77.4)	681	(30.3)	3923	(30.2)	194	(60.4)	1165	(48.8)	53	(51.5)	570	(66.5)
Co-medication with two or more QT-prolonging drugs	166	(34.9)	2541	(60.0)	27	(14.7)	72	(8.0)	37	(32.7)	243	(33.5)	174	(7.7)	1271	(9.8)	58	(18.1)	198	(8.3)	28	(27.2)	256	(29.9)
Most frequently used QT-prolonging co-medication																								
Escitalopram	17	(3.6)	345	(8.1)	2	(1.1)	9	(1.0)	5	(4.4)	25	(3.4)	75	(3.3)	395	(3.0)	6	(1.9)	43	(1.8)	2	(1.9)	24	(2.8)
Fluconazole	17	(3.6)	30	(0.7)	10	(5.4)	23	(2.6)	0	(0.0)	0	(0.0)	72	(3.2)	311	(2.4)	33	(10.3)	93	(3.9)	6	(5.8)	14	(1.6)
Ondansetron	28	(5.9)	99	(2.3)	23	(12.5)	61	(6.8)	13	(11.5)	62	(8.6)	221	(9.8)	489	(3.8)	119	(37.1)	687	(28.8)	5	(4.9)	24	(2.8)
Domperidone	185	(38.9)	2446	(57.7)	22	(12.0)	87	(9.7)	56	(49.6)	495	(68.3)	269	(12.0)	2192	(16.9)	63	(19.6)	324	(13.6)	32	(31.1)	347	(40.5)
Clarithromycin	-	-	-	-	1	(0.5)	1	(0.1)	3	(2.7)	3	(0.4)	43	(1.9)	759	(5.8)	11	(3.4)	37	(1.5)	23	(22.3)	323	(37.7)
Azithromycin	3	(0.6)	3	(0.1)	1	(0.5)	1	(0.1)	-	-	-	-	18	(0.8)	137	(1.1)	2	(0.6)	6	(0.3)	6	(5.8)	47	(5.5)
Itraconazole	131	(27.5)	2460	(58.0)	2	(1.1)	2	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Ciprofloxacin	43	(9.0)	759	(17.9)	14	(7.6)	45	(5.0)	18	(15.9)	137	(18.9)	-	-	-	-	13	(4.0)	18	(0.8)	3	(2.9)	3	(0.4)
Erythromycin	1	(0.2)	1	(< 0.1)	-	-	-	-	1	(0.9)	1	(0.1)	14	(0.6)	45	(0.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Mirtazapine	20	(4.2)	131	(3.1)	7	(3.8)	35	(3.9)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Levofloxacin	11	(2.3)	37	(0.9)	0	(0.0)	0	(0.0)	2	(1.8)	6	(0.8)	13	(0.6)	18	(0.1	-	-	-	-	0	(0.0)	0	(0.0)
Moxifloxacin	23	(4.8)	323	(7.6)	0	(0.0)	0	(0.0)	6	(5.3)	47	(6.5)	3	(0.1)	3	(0.0)	0	(0.0)	0	(0.0)	-	-	-	-
Hypokalemia (<3.3 mmol/l)[1]	110	(23.1)	361	8.5)	16	(8.7)	37	(4.1)	18	(15.9)	36	(5.0)	321	(14.3)	982	(7.6)	58	(18.1)	136	(5.7)	24	(23.3)	61	(7.1)
Renal impairment with need for MQAB dose reduction[2]	87	(18.3)	724	17.1)	2	(1.1	2	(0.2)	-	-	-	-	660	(29.4)	3723	(28.7)	67	(20.9)	347	(14.5)	-	-	-	-
→ without recommended dose-reduction	16	(3.4)	29	(0.7)	0	(0.0)	0	-	-	-	-	-	91	(4.0)	236	(1.8)	15	(4.7)	54	(2.3)	-	-	-	-
ICD-10 diagnosis associated with elevated TdP risk	232	(48.7)	-	-	24	(13.0)	-	-	40	(35.4)	-	-	679	(30.2)	-	-	108	(33.6)	-	-	35	(34.0)	-	-

[1] K^+ < 3.3 mmol/l on day(s) of co-administration

[2] For clarithromycin if eGFR < 30 ml/min, for erythromycin if eGFR < 10 ml/min, for ciprofloxacin eGFR < 30 - 60 ml/min, for levofloxacin if eGFR < 20 - 50 ml/min

Table 3: ECG-monitoring in MQAB users at risk of TdP

	Macrolides						Quinolones					
	Clarithromycin		**Erythromycin**		**Azithromycin**		**Ciprofloxacin**		**Levofloxacin**		**Moxifloxacin**	
	Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations		Hospitalizations	
	n	%	n	%	n	%	n	%	n	%	n	%
Co-medication with at least one QT-prolonging drug[1]	259	(100)	48	(100)	65	(100)	632	(100)	180	(100)	52	(100)
Current / pretreatment ECG available[2]	**128**	**(49.4)**	**27**	**(56.3)**	**21**	**(32.3)**	**334**	**(52.8)**	**92**	**(51.1)**	**27**	**(51.9)**
--> Thereof administration during episode(s) of hypokalemia[3]	37	(14.3)	7	(14.6)	6	(9.2)	79	(12.5)	21	(11.7)	10	(19.2)
--> Thereof with ICD-10 codes predisposing for TdP	70	(27.0)	9	(18.8)	11	(16.9)	483	(76.4)	40	(22.2)	12	(23.1)
--> Thereof with renal insufficiency requiring dose adaptation	19	(7.3)	1	(2.1)	na	na	123	(19.5)	14	(7.8)	na	na
--> Thereof with supratherapeutic dosing	1	(0.4)	0	(0.0)	na	na	7	(1.1)	3	(1.7)	na	na
--> Thereof abnormal / long QT[4]	9	(3.5)	2	(4.2)	2	(3.1)	36	(5.7)	6	(3.3)	0	(0.0)
~~--> Thereof non-drug-related abnormal / long QT[5]~~	~~5~~	~~(1.9)~~	~~1~~	~~(2.1)~~	~~0~~	~~(0.0)~~	~~20~~	~~(3.2)~~	~~4~~	~~(2.2)~~	~~0~~	~~(0.0)~~
~~--> Thereof causality not assessable (no ECG while exposed to DDI)~~	~~0~~	~~(0.0)~~	~~1~~	~~(2.1)~~	~~0~~	~~(0.0)~~	~~10~~	~~(1.6)~~	~~1~~	~~(0.6)~~	~~0~~	~~(0.0)~~
~~--> Thereof suspected drug related abnormal QT~~	~~4~~	~~(1.5)~~	~~0~~	~~(0.0)~~	~~2~~	~~(3.1)~~	~~6~~	~~(0.9)~~	~~1~~	~~(0.6)~~	~~0~~	~~(0.0)~~
--> Thereof WHO / CIOMS causality 'possible' for DDI regarding TdP	3	(1.2)	0	(0.0)	0	(0.0)	3	(0.5)	1	(0.6)	0	(0.0)
No current / pretreatment ECG available[2]	**131**	**(50.6)**	**21**	**(43.8)**	**44**	**(67.7)**	**298**	**(47.2)**	**88**	**(48.9)**	**25**	**48.1**
--> Thereof with hypokalemia[3]	22	(8.5)	3	(6.3)	8	(12.3)	54	(8.5)	17	(9.4)	5	(9.6)
--> Thereof with ICD-10 codes predisposing for TdP	52	(20.1)	6	(12.5)	14	(21.5)	72	(11.4)	19	(10.6)	6	(11.5)
--> Thereof with renal insufficiency requiring dose adaptation	20	(7.7)	1	(2.1)	na	na	73	(11.6)	14	(7.8)	na	na
--> Thereof with supratherapeutic dosing	1	(0.4)	0	(0.0)	na	na	5	(0.8)	2	(1.1)	na	na

[1] After exclusion of patients without consent to access original medical records
[2] Current / pretreatment ECG available = ECG performed up to 7 days before co-administration of studied AB with drugs known to cause TdP
[3] K^+ < 3.3 mmol/l on day(s) of co-administration
[4] Abnormal QTc = 450 ms for men / 460 ms for women; long QTc = > 500ms
[5] Presence of left bundle branch block / pacing pacemaker / use of amiodarone and (except AB) no other QT prolonging drugs
na = not applicable

Table 4: Adverse drug reactions associated with potential medication errors in MQAB users

Case code	*Sex*	*Age*	*Antibiotic(s)*	*Dose Antibiotic*	*Additional QT prolonging drug(s)*	*Dose additional drug(s)*	*Route of admin. AB*	*Route of admin. QT drug*	*Lung transplant*	*QTc*	*K^+*	*Mg^{2+}*	*Heart rate*	*CV diagnoses*
QT1	m	51	clarithromycin, azithromycin, ciprofloxacin	250 mg/3x per week	domperidone, ondansetron	30 mg/d, 4 mg/d	p.o.	p.o.	yes	491	3.3	0.98	90	-
QT2	f	67	clarithromycin	500 mg/d	domperidone	30 mg/d	p.o.	p.o.	yes	486	4	0.87	68	multiple heart diseases
QT3	m	47	clarithromycin	1000 mg/d	ondansetron	8-16 mg/d	i.v.	i.v., p.o.	no	484	4.3	-	55	-
QT4	m	42	levofloxacin	500 mg/d	ondansetron	24 mg/d	i.v.	i.v.	no	481	4.3	0.85	81	-
QT5	f	80	ciprofloxacin	500 mg/d	citalopram	40 mg/d	p.o.	p.o.	no	513	3.3	0.66	90	-
QT6	m	78	ciprofloxacin	800 mg/d	dipiperon, haloperidol (fix)	120 mg/d, 2 mg/d	i.v.	p.o.	no	518	-	1	61	multiple heart diseases
QT7	f	68	ciprofloxacin, azithromycin	250 mg/3x per week	ciprofloxacin, domperidone, citalopram	500 mg/d, 30 mg/d, 10 mg/d	p.o.	p.o.	yes	478			78	cardiomyopathy

Supplementary Table 1: Study population including patient-days

	Hospitalizations		*Patient-days*	
	n	(%)	*n*	(%)
All analyzed MQAB users	**3240**	**(100)**	**20721**	**(100)**
Sex				
Male	1913	(59.0)	12296	(59.3)
Female	1327	(41.0)	8425	(40.7)
Age distribution				
<18	14	(0.4)	69	(0.3)
18-44	694	(21.4)	4106	(19.8)
45-64	1195	(36.9)	8537	(41.2)
65-84	1205	(37.2)	7272	(35.1)
≥85	132	(4.1)	737	(3.6)
Use of studied antibiotics				
Macrolides				
Clarithromycin	476	(14.7)	4238	(20.5)
Erythromycin	184	(5.7)	901	(4.3)
Azithromycin	113	(3.5)	725	(3.5)
Quinolones				
Ciprofloxacin	2247	(69.4)	12989	(62.7)
Levofloxacin	321	(9.9)	2389	(11.5)
Moxifloxacin	103	(3.2)	857	(4.1)
Units with highest use of MQAB				
Urology	677	(20.9)	2366	(11.4)
Viszeral- and transplantation surgery	386	(11.9)	1895	(9.1)
Internal medicine	381	(11.8)	1601	(7.7)
Pneumology	271	(8.4)	3671	(17.7)
Haematology	170	(5.2)	1551	(7.5)
Most frequent primary ICD-10 diagnoses for hospitalizations with MQAB use				
Malignant neoplasms of lymphoid, hematopoietic and related tissue C81-C96	177	(5.5)	-	-
Complications of surgical and medical care, not elsewhere classified T80-T88	151	(4.7)	-	-
Other diseases of the urinary system N30-N39	142	(4.4)	-	-
Influenza and pneumonia J09-J18	139	(4.3)	-	-
Malignant neoplasms of digestive organs C15-C26	127	(3.9)	-	-